UK Journal of Pharmaceutical and Biosciences
Available at www.ukjpb.com
ISSN: 2347-9442

Meta-analysis to Assess Role of Systemic Antibiotics in Root Canal Treatment

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Article Information
Received 30 June 2017
Received in revised form 23 August 2017
Accepted 24 August 2017

Keywords:
Root canal treatment,
Antibiotics preference,
Susceptibility,
Oral pathogens

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Abstract

The role of systemic antibiotics in root canal treatment (RCT) always remained controversial. To exactly identify the state of affairs, regarding whether or not the usage of systemic antibiotics in RCT, the current meta analysis was carried out. To identify the frequency of discouraging or preferring the use of systemic antibiotics in RCT. Secondly to identify the efficacy of various antibiotics in post RCT infections. Department of Operative Dentistry, Rawal Dental College Islamabad and Pathology Department of Al Nafees Medical College & Hospital, Isra University Islamabad Campus, Pakistan. Total 41 published studies in 03 and a half decades were included in the study i.e 1981 – 2017. Various authentic electronic sources were used to gather adequate and authentic data by simple random sampling technique. 66.6%(n=08) studies from 1987 till 2011, were not in favour of using systemic antibiotics as a part of RCT. While 33.3% (n=04) preferred using systemic antibiotics for RCT. Regarding the local antibiotic preference, 33.3% (n=04) studies were in favour of using a combination of triple antibiotic paste comprising of metronidazole, minocycline and ciprofloxacin. There is no role of systemic/local antibiotics in endodontic management. However, the use of antibiotics is only recommended if deemed necessary by viewing the premorbid of patient.

1 Introduction

The focal infection theory was established in early 1900s and hence restricted the evolvements in field of endodontics. The theory described that a foci of microorganisms or their enzymes and toxins can easily disseminate systemically. The resultant can manifest as either extensive tissue damage or systemic infection. The theory was rejected afterwards because of limited authentic supportive evidence. In year 2000 certain proven associations were established amongst dental infection with cardiovascular disorders, rheumatoid arthritis and many other systemic illnesses and complications. The documentary evidence was also provided to support that the cultivated bacteria from peripheral blood and the one present at the site of root canal treatment (RCT) were the same[1]. Jayakodhi H in 2012 also supplemented this finding that the involved bacteria are primarily the ones infecting root canals related with periradicular lesions[2].The presence of Interappointment pain and swelling i.e flareups in pulp or periradicular tissues, are the initial symptoms following RCT to comprehend a microbial, mechanical or chemical etiology. The incidence of microbial etiology is on the top amongst all these[2]. The reason behind could be the incomplete or over instrumentation resulting in endodontic microbiota changes, apical extrusion of debris and could be secondary intraradicular infections[3]. Furthermore the management options for this includes premedication, relief of occlusion, drainage establishment, use of intracanal and systemic medication. The commonly involved bacteria for symptomatic periradicular lesions and flareups includes *Porphyromonas gingivalis*, *Porphyromonas endodontalis, Fusobacterium nucleatum*, *Prevotella* species, *Porphyromonas* species, Streptococcus mutans, Enterococcus feacalis[4,5].

The use of systemic antibiotics always remained controversial. Fouad AF *et al* in 2002 concluded that usage of systemic antibiotics harbours no justification[6]. The observations was supplemented by *Nabavizadeh MR et al in 2011.* He concluded the successful outcomes of RCT can well be achieved by intervening either through mechanical/chemical cleaning or via surgical procedure[7]. *Weber JT et al in 2005* also discouraged

the use of systemic antibiotics in RCT and preferred mechanical and chemical cleaning of root canal[8-10]. He also concluded that antimicrobial resistance, drug interaction, several side effects i.e nausea, vomiting, gastrointestinal upsets, allergic reactions and antibiotic associated colitis are the main reasons for discouraging systemic antibiotic usage in RCT[7,8]. Many other studies i.e by *Palmer NA et al* in 2001, *Yingling NM et al* in 2002 and *Tabrizizade M et al* in 2005 preferred using antibiotics for flareup reactions. The use of amoxil, penicillin V, clindamycin, erythromycin and metronidazole were preferred by them[11-13].

In light of available literature, the current meta analysis was planned to identify the actual situation regarding whether or not the usage of systemic antibiotics in RCT.

2 Materials and Methods

2.1 Search methods A total 41 published studies in 03 and a half decades were included in the study i.e 1981 – 2017. Various authentic electronic sources were used to gather adequate and authentic data by simple random sampling technique. The National and Internationally published data was thoroughly reviewed for the current meta analysis.

To maintain the *Quality Criteria,* the published data was gathered from Pak Medinet.com, Medscape, Pubmed, Embase, Cochrane, Medline, Google search, British, and Canadian guidelines.

For *quality criteria* and based upon the study objectives, six aspects were identified and distributed amongst five authors of current manuscript. The MeSH terms were used for searching the relevant data. These six aspects are mentioned below;

1. Published studies in favour of discouraging or preferring the use of systemic antibiotics in RCT.
2. Published studies in favour of discouraging or preferring the use of local antibiotics in RCT.
3. Sensitivity pattern of antibiotics for patients having post RCT infections.
4. Resistant pattern of antibiotics for patients having post RCT infections.
5. Sensitivity pattern of antibiotics for various bacteria/ pathogens in patients having post RCT infections.
6. Resistant pattern of antibiotics for various bacteria/ pathogens in patients having post RCT infections.

The finally selected manuscripts were identified after the consensus of all five authors.

2.2 Inclusion criteria The published authentic guidelines, case reports, short communications, original and review articles were included in the study.

2.3 Exclusion criteria Letters to editor, and editorials were excluded.

2.4 Data analysis The statistical analysis of published researches was done by using SPSS version 19. Frequencies were calculated in terms of percentages for quantitative variables.

3 Results

Total 41(N) studies were included in the study. The statistics discouraging or preferring systemic/ local antibiotics for RCT are shown in table 1. Out of total 12 (n) published studies, 66.6%(n=08) from 1981 till 2011, were not in favour of using systemic antibiotics as a part of RCT. While 33.3% (n=04) preferred using systemic antibiotics for RCT. Regarding the local antibiotic preference, 33.3% (n=04) studies were in favour of using a combination of triple antibiotic paste comprising of metronidazole, minocycline and ciprofloxacin. The details are shown in table 1.

The studies supporting the sensitive pattern of systemic and local antibiotics in post RCT infections are shown in table 2. Regarding the penicillin group of antibiotics, statistic for four drugs were noticed i.e amoxil, amoxicillin, augmentin and penicillin V.

Nabavizadeh MR in 2011 and Palmer NA in 2001 concluded that amoxil is a drug of choice for any sort of post RCT infection. Palmer NA identified 47.3% sensitivity to amoxil. Yingling NM in 2002 and Roda R in 2007 concluded 67.8% each, sensitivity of amoxil. Roda R in 2007 concluded that amoxixillin harbours good sensitivity pattern for treating post RCT infections. Gamal M in 2015 declared augmentin a highly sensitive antibiotic. Yingling NM in 2002, Tabrizizade M in 2005, Morcillo E in 1997,and Skucaite N in 2010 concluded that penicillin V the drugs of choice for post RCT infections.

Regarding macrolide group, erythromycin was the commonly tested antibiotic. Tabrizizade M in 2005 (70.4% sensitivity), Morcillo E in 1997, Skucaite N in 2010, and Gamal M in 2015 concluded that erythromycin is the drug of choice for post RCT infections.

Regarding lincosamide group (bactericidal ones), clindamycin was the most commonly seen sensitive antibiotic. A study report by Yingling NM in 2002 showed 57.3% sensitivity. While other reported studies i.e Sobottka I in 2002, Swift JQ in 2002, Addy LD in 2005 and Skucaite N in 2010 also declared clindamycin a drug of choice for treating post RCT infections.

Table 1: Statistics Discouraging or Preferring Systemic/ Local Antibiotics for RCT (N=12)

Studies	Studies supporting the use or disuse of systemic/local antibiotics		
	Against The Use of Systemic Antibiotics	Favour of Using Systemic Antibiotics	Favour of Using Local Antibiotics
Fouad AF et al (2002)[6]	Not preferred	-	-
Nabavizadeh MR (2011)[7]	Not preferred	-	-
Barker GR (1987)[8]	Not preferred	-	-
Palmer N (1998)[9]	Not preferred	-	-
Palmer NA (2001)[10]	-	Preferred	-
Yingling NM (2002)[11]	-	Preferred	-
Tabrizizade M (2005)[12]	-	Preferred	-
Sato I (1996)[17]	Not preferred	-	Preferred local triple antibiotic pastes
Dhillon JS (2014)[27]	Not preferred	-	Preferred local triple antibiotic pastes(metronidazole, minocycline and ciprofloxacin)
Taneja S (2011)[28]	Not preferred	-	Preferred local triple antibiotic pastes
Mohammadi Z (2009)[29]	Not preferred	-	Preferred local triple antibiotic pastes
Roda R (2007)[31]	-	Preferred	-

Regarding the local antibiotics, the study reports by Dhillon JS (2014), Taneja S (2011), Mohammadi Z (2009) and Sato I (1996) concluded a sensitive pattern for metronidazole, ciprofloxacin and minocycline (only when used in combination).

Amongst the list flouroquinolones, ciprofloxacin is the drug of choice declared sensitive by Sobottka I in 2002.

Roda R in 2007 declared linezolid (oxazolidinone i.e protein inhibitor) a sensitive one for post RCT infections.

Regarding tetracyclines, doxycycline and minocycline were the two tested drugs. Sobottka I in 2002 and Skucaite N (2010) declared doxycycline a sensitive one for treating post RCT infections.

Skucaite N in 2010, and Gamal M in 2015 concluded that vancomycin (glycopeptide group) is a sensitive drug for post RCT infections.

The studies supporting the resistant pattern of systemic and local antibiotics in post RCT infections are shown in table 3. Studies done by Roda R and Sobottka I in 2002 and 2007, concluded resistant pattern to amoxicillin. Penicillin V, Erythromycin and Clindamycin were declared resistant by Aracil B and Groppo FC in 2001 & 2005. The National UK formulary guidelines professed Clindamycin as having resistant pattern.

Metronidazole and Tetracyclines were declared resistant by Gamal M in 2015. Regarding the resistant pattern of metronidazole Skucaite N in 2010 also concluded the same resistant pattern for anaerobes.

The details of antibiotic susceptibility reported in various studies for oral microbes is shown in table 4. Vancomycin harbours 100% sensitivity for oral pathogens in post RCT. The findings were described in study carried out by Skucaite N in 2010. This finding was supported by Gamal M in 2015. He also declared vancomycin a drug of choice.

Penicillin G harbours 100% sensitivity for *Porphyromona species*. The findings were described in a study carried out by Skucaite N in 2010. Morcillo E in 1997 supported this observation.

Clindamycin harbours 100% sensitivity for anaerobes. The findings were described in a study carried out by Skucaite N in 2010. It was further strengthened by studies carried out by Canadian guidelines in 2001, Sobottka I in 2002, Swift JQ in 2002, Addy LD in 2005, and Skucaite N in 2010. All of those studies declared clindamycin a drug of choice for all oral pathogens.

Next in sequence are the Quinolones. Sobottka I in 2002 disclosed 98% sensitivity for oral pathogens in post RCT.

Table 2: Susceptibility Pattern of Systemic & Local Antibiotics for Treating Post RCT infections

Studies	AM	AX	AG	PC	ET	CD	MZ	CF	MC	LZ	DC	VC
Nabavizadeh MR(2011)[7]	Drug of choice	-	-	-	-	-	-	-	-	-	-	-
Palmer NA (2001)[10]	Drug of choice (47.3%)	-	-	-	-	-	-	-	-	-	-	-
Yingling NM (2002)[11]	Drug of choice (67.8%)	-	-	Drug of choice (61.4%)	-	Drug of choice (57.3%)	-	-	-	-	-	-
TabrizizadeM(2005)[12]	-	-	-	Drug of choice (60.6%)	Drug of choice (70.4%)	-	-	-	-	-	-	-
Sato I (1996)[17]	-	-	-	-	-	-	Preferred local triple antibiotic pastes-			-		-
Gamal M (2015)[21]	-	-	S	-	S	-	-	-	-	-	-	S
Skucaite N (2010)[22]	-	-	-	S	S	S	-	-	-	-	S	S
Dhillon JS (2014)[27]	-	-	-	-	-	-	Preferred local triple antibiotic pastes			-	-	-
Taneja S (2011)[28]	-	-	-	-	-	-	Preferred local triple antibiotic pastes			-	-	-
Mohammadi Z (2009)[29]	-	-	-	-	-	-	Preferred local triple antibiotic pastes			-	--	-
Roda R (2007)[31]	67.8% S	S	-	-	-	-	-	-	-	S	-	-
Sobottka I (2002)[32]	-	-	-	-	-	S	-	S	-	-	S	-
Swift JQ (2002)[33]	-	-	-	-	-	S	-	-	-	-	-	-
Addy LD (2005)[34]	-	-	-	-	-	S	-	-	-	-	-	-
Morcillo E (1997)[35]	-	-	-	S	-	-	-	--	-	-	-	-

Amoxil-AM, Amoxicillin-AX, Augmmentin-AG, PenicillinV-PC, Erythromycin-ET, Clindamycin-CD, Metronidazole-MZ, Ciprofloxacin-CF, Minocycline-MC, Linezolid-LZ, Doxycycline-DC, Vancomycin-VC

Roda R in 2007 concluded that linezolid was 95% sensitive for oral biofilm in post RCT infections.

The sensitivity details of augmentin, erythromycin and tetracycline/ doxcycline are also shown in table IV.

The details of resistant pattern of various antibiotics in relation to oral microbes are shown in table IV. UK guidelines for the year 2002 strongly discouraged the use of clindamycin. Whereas the statistics of different researches regarding resistant pattern of various antibiotics are also tabulated in table 4.

4 Discussions

Out of total 12 (n) published studies i.e 66.6% studies from 1987 till 2011, were not in favour of using systemic antibiotics as a part of RCT. The recommended UK guidelines (2002) for systemic antibiotics usage in RCT are strongly discouraged. However it was clarified that the systemic antibiotics should only be used in patients at risk for infective endocarditis[14]. In the advancing era systemic antibiotics are recommended only if there are features for systemic infections or re-implantation of an avulsed tooth[15-17].

Barnes J et al in 2011 described that in 1770s and 1980s increased understanding for the microbiology of infected root canal was identified[18]. Over the past two decades that knowledge was built upon and good understanding was

established for microbial biofilm, etiological factors for infections, and the associated factors for successful outcome or failure of root canal[19]. Achieving successful sterilization during RCT always remained a challenging task for the clinicians resulting in failure of RCT. The highlighted reasons includes presence of various microorganisms and the polymicrobial infections[20].

Table 3: Resistant Pattern of Systemic & Local Antibiotics For Treating Post RCT infections

Studies	Amoxicillin	Penicillin V	Erythromycin	Clindamycin	Metronidazole	Tetracycline
Yingling NM (2002)[11]	-	-	R	-	-	-
Gamal M (2015)[21]	-	-	-	-	R	>36% R
Skucaite N (2010)[22]	-	-	-	-	>56% R	-
Roda R (2007)[31]	R	-	-	-	-	-
Sobottka I (2002)[32]	R	-	-	-	-	-
UK guideline(2002)[35]	-	-	-	R	-	-
Aracil B (2001)[40]	-	R	R	R	-	-
Groppo FC (2005)[41]	-	R	R	R	-	-

Gamal M et al in 2015 conducted a study on patients having post RCT infection. The commonly detected isolates were *Enterococcus faecalis* 15%, *Streptococcus mutans* 9.5%, *Streptococcus acidominimus* 8.7% and *Porphyromonas gingivalis* 7.93%. The antimicrobial sensitivity for these microbes revealed amoxicillin-clavulanic acid, erythromycin and vancomycin the ideal choices. Resistant pattern to tetracycline was observed in 36.50 % cases[21].

The injudicious use of systemic antibiotics by dental practitioners should be discouraged. They are adding up to the economical burden and emergence of drug resistance strains. Moreover a patient has to bear severe side effects[22-25].

The results extracted from current meta analysis revealed that out of total 16 (n) studies, 12(n) were in favour of using systemic antibiotics, while 04(n) supported the use of local triple antibiotic paste. This is supported by a study report by *Dhillon JS et al in 2014,* which revealed successful outcome by applying triple antibiotic paste locally. This paste comprises a combination of metronidazole, ciprofloxacin, and minocycline[26]. Tracing back, the studies done by *Taneja S et al in 2011, Mohammadi Z et al in 2011* and *Sato I et al in 1996* were aligned with conclusions of *Dhillon JS et al*. They also found this triple antibiotic paste a very effective modality to eliminate endodontic pathogens.

However, because of impending risks of side effects by systemic antimicrobial, their use is discouraged. All these three studies narrated, that because of diversity in micro flora i.e aerobic and anaerobic, missing anyone of three above mentioned antibiotics will reduce the efficacy of treatment[27-29]. *Swathi PA et al in 2014* conducted a study on diabetic patients undergone RCT, he concluded that infection rate was negligible in the group of patients where triple antibiotic paste as intercanal medication was used[30].

Contrary the study by *Roda R et al in 2007* for Valencian community (Spain) showed that augmentin (amoxixillin plus clavunic acid) is the most commonly prescribed drug. He also described that there 10% of all antibiotic prescriptions are because of dental infections[31].

The current meta analysis concluded that vancomycin, flouroquinolones, linezolid, and penicillin G were the ideal drugs for managing post RCT infections. This finding is supported by the published data. *Sobottka et al in 2002* concluded that flouroquinolones, doxycycline and clindamycin are the drugs of choices for successful management of dental infection. However, amoxicillin is having high resistant pattern for oral bacteria [32].

Swift JQ, et al (2002) described that clindamycin because of it specific pharmacokinetic and pharmacodynamics properties, harbours excellent tissue and bone penetration properties. Therefore it can be an ideal drug for managing all dental infection[33].

Addy LD et al in 2005 concluded from his study that clindamycin is a drug of choice for endodontic procedures[34]. Contrary Dental Practitioner's Formulary (DPF) of UK discourages the use of clindamycin because of a serious side effect i.e pseudomembranous colitis[35, 36]. However the Canadian guidelines recommends the use of clindamycin[36,37]. *Morcillo E et al in 1997* concluded that despite the advancement in antimicrobials, none is worth enough to replace the penicillin group for managing dental infections[38].

Like many other microbes for systemic infections, a trend of resistant pattern emergence is seen for the pathogenic oral bacteria[39]. Penicillins, macrolides and clindamycin are the reported drugs showing resistant pattern to *Porphyromona apecies, Prevotella species, Streptoccocus viridans*[40,41].

Table 4: Sensitive & resistant pattern of antibiotics against various isolates (post RCT infection)

Studies	Drugs	*PS*	*PRS*	*SV*	*FN*	*PSS*	*AS*	*EC*
Sensitive antibiotics against various isolates								
Gamal M(2015)[21]	AG	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
	ET	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
	VC	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
Skucaite N (2010)[22]	VC	100%	100%	100%	100%	100%	100%	-
	PG	100%	-	72.1%	-	-	-	81%
	CD	74%	74%	86%	74%	74%	100%	74%
	ET	-	-	65%	-	-	-	-
	TC	-	-	58%	-	-	-	70%
	QL	>98%	>98%	>98%	>98%	>98%	-	-
Sobottka I (2002)[32]	CD	70-75%	70-75%	70-75%	70-75%	70-75%		
	DC	70-75%	70-75%	70-75%	70-75%	70-75%		
Roda R (2007)[31]	LZ	>95%	>95%	>95%	>95%	>95%	-	-
Swift JQ (2002)[33]	CD	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
Addy LD(2005)[34]	CD	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
Canadian guidelines (2001)[36]	CD	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
Morcillo E (1997)[38]	PL	Drug of choice	Drug of choice	Drug of choice	Drug of choice	Drug of choice	-	-
Resistant antibiotics against various isolates								
Studies	Drugs	***PS***	***PRS***	***SV***	***FN***	***PSS***	***AS***	***EC***
Gamal M (2015)[21]	TC	R >36%	Resistant	Resistant	Resistant	Resistant	-	-
	MZ	Resistant	Resistant	Resistant	Resistant	Resistant	-	-
Skucaite N (2010)[22]	MZ	Resistant	Resistant	Resistant	Resistant	Resistant	>56%	-
	ET	-	-	-	-	-	-	10%
Roda R (2007)[31]	AX	-	<25%	-	-	-	-	-
Sobottka(2002)[32]	AX	30-80%	30-80%				-	-
UK guidelines (2002)[35]	CD	Not preferred	Not preferred	Not preferred	Not preferred	Not preferred	-	-
Aracil B (2001)[40]	PL	Resistant	Resistant	Resistant	-	-	-	-
	ET	Resistant	Resistant	Resistant	-	-	-	-
	CD	Resistant	Resistant	Resistant	-	-	-	-

Amoxicillin-AX, Augmmentin-AG, Erythromycin-ET, Clindamycin-CD, Metronidazole-MZ, Linezolid-LZ, Doxycycline-DC, Vancomycin-VC, Penicillin-PL, Penicillin G-PG, Tetracycline-TC, Quionlones-QL; *Porphyromona spp-PS, Prevotella species-PRS, S. viridans-SV, F. nucleatum-FN, Pepto streptococcus spp-PSS, Anaerobes-AS, Enterococci-EC*

The thorough literature review for this meta analysis showed that the use of systemic antibiotics followed by RCT should be

discouraged. Necessitating the adoption of strict sterilization and disinfection protocols for successful outcomes of RCT.

5 Conclusion

There is no role of systemic/local antibiotics in endodontic treatment. It is discouraged, unnecessary and inappropriate. However, the use of antibiotics is only recommended if deemed necessary by viewing the premorbid of patient. Flouroquinolones, linezolid, penicillin G and vancomycin harbours good susceptibility for endodontic infections. While metronidazole, macrolides and tetracyclines are resistant to oral pathogens.

6 Recommendations

- Strict protocols/guidelines for sterilization/ disinfection, to be followed for RCT
- The prescription protocols/ guidelines to be reviewed for endodontic procedures.
- The justification of choice and dose of antibiotics should be appropriate to avoid emergence of drug resistance strains.
- If deemed necessary a paste of tripple local antibiotics i.e metronidazole, ciprofloxacin and minocycline should be used for RCT before starting systemic antibiotics.
- Elaborated studies should be carried out for assessing the sensitivity patterns of carbapenams, cephalosporins, and aminoglycosides to manage serious endodontic infection.

7 Limitations of study

Data was limited for the susceptibility pattern of carbapenams, cephalosporins, and aminoglycosides

8 Conflicts of interests

There are no conflicts of interests regarding publication of this manuscript.

9 Author's contributions

NN: Provoking the idea of manuscript, Gathering and compiling the data for Published studies in favour of discouraging or preferring the use of systemic antibiotics in RCT.

SH: Gathering and compiling the data for Published studies regarding sensitivity & resistant pattern of antibiotics for patients having post RCT infections.

HZ: Compiling and formulating the entire manuscript by summarizing abstract, introduction, methodology, results and discussion.

NKL: Gathering and compiling the data for Published studies regarding sensitivity pattern of antibiotics for various bacteria/ pathogens in patients having post RCT infections.

KTB: Gathering and compiling the data for Published studies regarding resistant pattern of antibiotics for various bacteria/ pathogens in patients having post RCT infections.

10 Funding resources

None to disclose

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